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EXAMINER

WOITACH, JOSEPH T

ART UNIT PAPER NUMBER

1632

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/435,629

Applicant(s)

STICE ET AL.

Examiner

Joseph T. Woitach

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 91-95, 97-100 and 103-105 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 91-95, 97-100, 103-105 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

This application filed November 8, 1999, is a divisional of 08/766,939, filed December 16, 1996, now US Patent 5,994,619, which is a continuation in part of 08/626,054, filed April 1, 1996, now US Patent 5,905,042.

Applicants' amendment filed April 19, 2004, has been received and entered. Claims 1-90, 96, 101, 102 and 106-120 have been canceled. Claim 97 has been amended. Claims 91-95, 97-100, 103-105 are pending.

Election/Restriction

Applicant's election without traverse of group II, drawn to a stable culture/cell line of cultured inner cell mass cells capable of prolonged passage, (see Paper No. 9) was acknowledged. Claims encompassing non-elected inventions have been canceled.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

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Double Patenting

The objection under 37 CFR 1.75 of claims 101 and 102 as being a substantial duplicate of claim 91 is withdrawn.

Cancellation of claims 101 and 102 has obviated the basis of the objection. It is noted that Applicants argue that claims 101 and 102 are not a duplication of claim 91, however have not provided any specific reasoning to support the assertion (see Applicants amendment, bottom of page 5). As stated in the previous office action, the teaching of the present specification teaches that the structural and physical characteristics of bovine CICM cells (claim 101), and the markers of alkaline protease positive and cytokeratin 18 negative (claim 102) are inherent properties used to identify CICM cells. While the objected claims have been canceled it is noted that setting forth any physical characteristics and specific markers that are inherently present on CICM cells would not further limit the scope of CICM cells being claimed because they encompass exactly the same subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 91-95, 97-100, 103-105 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 91-95, 97-100, 103-105 also stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Applicants note that "methods for producing transgenic CICM cell lines start with genetically identical cells (derived from a NT unit), which are then transfected with a transgene that expresses a desired gene" (Applicants' amendment page 6). Examiner notes that the present claims are not directed to a product by process and thus are not limited by any particular methodology such as being produced by nuclear transfer methodology. Since transgenic cell lines do not exist in nature, by implication the claimed compositions must be obtained through some sort of genetic manipulation, however it is not limited to the use of nuclear transfer methodology for making clones.

Applicants note that "unless transfection and selection is 100% the method will inevitably give rise to genetically identical population of cells except for the fact that some will contain and express the transgene and some will not" and argue that expression will vary dependent on where

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the transgene becomes integrated. (Applicants' amendment, page 6). Initially, it is noted that the time and means of inserting the transgene into a cell has not been set forth nor limited in the claimed composition. Moreover, the specification does not describe a single method for transfection and selection or a required means for making a cell line. Beyond the fact that Applicants are arguing about features (i.e., produced with NT methods, genetically identical, different transgene expression because of insertion site) that are not recited in the rejected claim(s), and though the claims are interpreted in light of the specification, limitations from the specification are not read into the claims (See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993)). More importantly, the limitations relied upon are not in the specification nor are they an absolute consequence because they rely on the specific methodology used. For example, in methods known in the art produce a cell line from a single cell clone there would be no difference in the insertion site of a transgene. Applicants note that the Examiner has "made the rejection based on the fact that the disclosure allegedly does not provide literal support for the claims" but argue that "this is not the legal standard" and "[A]ll that the law requires is that the specification clearly convey that the inventors were in possession of the invention based on the as-filed application" (Applicants' amendment, bridging pages 6-7). Pointing to a single working example on page 41 where selection under certain specific conditions was not complete, Applicants argue that the "skilled artisan would draw based on these explicit teachings that the transgenic procedure results in a mixed population of genetically identical CICM cells except for the expression or non-expression of a particular transgene" (Applicants' amendment, page 7).

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First, as noted above, CICM cells can be made by any variety of methods known in the art at the time of filing and are not limited to the example provided in the instant specification. This interpretation is supported by Applicants own specification also on page 41 which states that “the transgenic CICM cell can be selected for by several procedures.” With respect to the example relied upon by Applicants’ it is also noted that cells that survived all contained and expressed the GEO construct otherwise they would not have survived the selection process, therefore represents a single population of cells all expressing the transgene. It is not clear why the artisan would conclude from this example that there were cells that contained the construct, however it was not expressed because there does not seem to be any evidence to this fact. To the contrary, PCR was used to confirm that all cells that survived selection had the construct. In addition, it is not clear that the skilled artisan would consider a resulting population of cells that contain a transgene at different locations in the chromosome(s) genetically the same because the genomes would not be identical. Applicants’ arguments are not found convincing because it appears that Applicants are attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

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As noted above there appears to be no literal support in the specification for the instant claims and Applicants only support appears to be the figurative support provided by working examples. The figurative support pointed to by Applicants in the specification provides CICM cells with or without a transgene, not a genetically identical cell line or a transgenic cell line that demonstrates heterologous expression patterns. In each case, the specification provides no support for generating or using the instantly claimed composition. As reasoned in the previous office action, the instant situation is analogous to *Gentry Gallery, Inc. v. Berkline Corp.*, 134_F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998) where under certain circumstances, omission of a limitation can raise an issue regarding whether the inventor had possession of a broader, more generic invention. (In *Gentry Gallery*, the "court's determination that the patent disclosure did not support a broad meaning for the disputed claim terms was premised on clear statements in the written description that described the location of a claim element--the control means' --as the only possible location' and that variations were outside the stated purpose of the invention.' *Gentry Gallery*, 134_F.3d at 1479, 45 USPQ2d at 1503. In the instant case, while *in vitro* transfection methods may result in some cells receiving and expressing a heterologous polynucleotide and some cells not expressing the transgene, there is no clear indication that the instantly claimed invention was specifically contemplated anywhere in the instant specification.

As stated in the previous office action, the composition of totipotent transgenic cells comprising two populations of cells one which expresses a transgene and one that does not

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express a transgene is considered new matter. Applicants have failed to point to literal support for the embodiment and the working example relied upon by Applicants would not even make the embodiment obvious because the method of selection is specifically used to obtain a cell or population of cells that all have and express the selectable marker, and is contrary to providing the mixed population as instantly claimed. In this amendment, Applicants have not relied upon the results in Example 5 which describes the differentiation of CICM cells, but as noted previously this does not support totipotent cells which differentially express a gene of interest. Upon review of the specification, the only compositions which have the ability to differentially express a gene are compositions of cells which genetically different which were combined to provide a chimeric composition of cells.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. In the instant case a review of the claims and portions of the specification pointed to by Applicants does not support the limitations presently set forth in the claims. Further, a review of

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the entire specification the only compositions which meet the limitations set forth in the present claims are compositions of genetically different cells. The present specification fails to provide literal or figurative support for a transgenic totipotent bovine CICM cell line which contains two populations of cells, one which expresses and one that does not express the transgene in said cell line.

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 91, 96 and 97 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expressing the differentiation-inhibiting gene LIF, does not reasonably provide enablement for any other of the genes specifically recited in the claims or the specification is withdrawn.

The amendment to the claims to delete any functional limitation of the transgene expressed has obviated the basis of the rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 91-95, 97-100, 103-105 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 91 is vague and confusing in the ability of

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the CICM cells from one cell line being capable of differentially expressing a transgene. It appears that all the cells contain the transgene in light of the recitation that the second CICM contains the transgene because of the limitation that it is not expressed. Further, it appears that both are totipotent, because the cells are from the same cell line and there is no indication that both populations of cells are not totipotent. Given that both populations are the same, it is unclear how one population of cells express a transgene and an identical population does not. Dependent claims do not further clarify the basis of the rejection because they only set forth how the CICM cells are specifically modified or cultured. These limitations further indicate that CICM cells are treated in the same manner, and none of these limitations provide a basis for obtaining two different gene expression patterns in one composition.

Applicants argue that the meaning of claims is not ambiguous and that two different cells one expressing a transgene and one not expressing a transgene are comprised by the claims (Applicants' amendment, page 8). Applicants' arguments have been fully considered but not found persuasive.

As reasoned in the previous office action the claims are not directed to a product by process, and because the same CICM cell line is required for both the CICM cell line that expresses a transgene and one that does not express a transgene, the claims fail to clearly indicate how a single cell can comprise at least two different properties. Examiner would acknowledge that the claims encompass two different populations, however in the context of the claimed invention as a whole it is unclear how these two populations could exist. For example,

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encompassed by the instant claims is a transgenic CICM cell line (claim 91) that has the transgene comprising the selectable marker β -GEO (claim 95) operatively linked to the constitutive CMV promoter (claim 98). Given this specific combination it is unclear how two different populations of expressing and non-expressing cells could exist. This evaluation would apply equally to any other promoter or any other gene of interest. The claims are vague and confusing in the ability of the CICM cells from one cell line being capable of differentially expressing a transgene. Again, it appears that all the cells contain the transgene in light of the recitation that the second CICM contains the transgene because of the limitation that it is not expressed. Further, it appears that both are totipotent, because the cells are from the same cell line and there is no indication that both populations of cells are not totipotent. Given that both populations are the same, it is unclear how one population of cells express a transgene and an identical population does not. Dependent claims do not further clarify the basis of the rejection because they only set forth how the CICM cells are specifically modified or cultured. These limitations further indicate that CICM cells are treated in the same manner, and none of these limitations provide a basis for obtaining two different gene expression patterns in one composition.

Therefore, for the reasons above and of record, the rejection is maintained.

Claim 97 recites the limitation "the D1 gene transgene" in the first line of the claim.

There is insufficient antecedent basis for this limitation in the claim or in claim 91. It is noted

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the claim was previously dependent on claim 96, however it has been amended to be dependent on claim 91 which has no literal support for any specific type of transgene such as D1 gene.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 91-95 and 103-105 stand rejected under 35 U.S.C. 102(e) as being anticipated by Sims *et al.* (US Patent 6,107,543).

Applicants argue that Sims *et al.* does not enable the claimed invention and fails to teach a mixed population of cells. Applicants' arguments have been fully considered, but not found persuasive. See Applicants amendment, page 8.

Initially, it is noted that there is no functional limitation in the instant claims to how long the claimed CICM cells must remain totipotent. Applicants assertion that the Sims *et al.* patent is not enabled is noted, however the working examples suggest and provide evidence to the contrary. Sims *et al.* provide guidance to optimize culture media and conditions to obtain undifferentiated cells in culture. Further, it should be noted that the instant specification defines CICM cells as cells which exhibit morphological and gene expression characteristics similar to ICM cells (page 15) Even though Sims *et al.* teach that the isolated cells can differentiate into

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particular cell types under specific conditions, the initial population and culturing conditions provided to keep the cells in culture enable and would provide cells that meet the limitations encompassed by claims.

Claims 91 and 92 encompass a composition of CICM cells wherein the cells contain a heterologous polynucleotide sequence. The dependent claims 93-95, 101 and 102 recite specific marker genes and specific properties of the cells and compositions which further comprise feeder cells. Sims *et al.* teaches ICM cells in culture. Sims *et al.* teach that the cells can be modified to contain any gene of interest, in particular selectable markers which result in selection against neomycin (columns 13-14). The inner cell mass cells (ICM) are capable of giving rise to blastocyst and live born calves (Table 1 and 4). Sims *et al.* teach similar methods for the isolation of inner ICM as those disclosed in the instant specification. Though Sims *et al.* do not specifically describe the specific morphology of the cells in culture or that the ICMs are alkaline protease positive and cytokeratin 18 negative, in light of the similarity of isolation techniques and similarity in other morphologies, the ordinary artisan would expect that the ICM cells of Sims *et al.* in '543 have the same characteristics as and that any specific properties would inherent. It is noted that where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant

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has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01. Finally, Sims *et al.* teach various methods of culturing the cells, including culturing the cells on feeder cells. Thus, the compositions of ICM cells taught by Sims *et al.* anticipate the claims. As indicated previously, upon review of instant disclosure and that of Sims *et al.* the methods for isolation and culturing CICM cells are very similar and one would expect that the resulting CICM cells would be identical to those describe in the present specification. Examiner would agree that Sims *et al.* did not reduce to practice a transgenic CICM cell or use said cell to generate a calf, however clearly Sims *et al.* had a reasonable expectation that this could be accomplished in providing the specific teachings for the introduction of a transgene. The guidance for the introduction of a transgene given in the present disclosure is not unique or novel. Further, it should be noted that the present specification does not reduce to practice a live calf which is capable or demonstrates that a transgene is contained in the germ cells of said animal, thus the instant disclosure does not reduce to practice experiments which clear demonstrate that the cell after selection or various culturing conditions was totipotent. Applicants' arguments as they apply to present rejection are not convincing because

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in light of the specific teachings of each of the specifications there was an expectation that CICM cells transduced with a gene of interest would still be totipotent.

Therefore, for the reasons above and of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).